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Synthesis of Pyrrolophenanthridine Alkaloids based on C(sp³)-H and C(sp²)-H Functionalization Reactions

Chihiro Tsukano, Nobusuke Muto, Iderbat Enkhtaivan, and Yoshiji Takemoto*[a]

Abstract: Assoanine (**1**), pratosine (**2**), hippadine (**3**) and dehydroanhydrolycorine (**4**) belong to the pyrrolophenanthridine family of alkaloids, which are isolated from plants of the Amaryllidaceae species. Structurally, these alkaloids are characterized by a tetracyclic skeleton containing a biaryl moiety and an indole core, and compounds belonging to this class have received considerable interest from researchers in a number of fields

because of their biological properties and the challenges associated with their synthesis. In this study, we have developed a strategy for the total synthesis of these alkaloids using C-H activation chemistry. The tetracyclic skeleton **5** was constructed in a stepwise manner by C(sp³)-H functionalization followed by a Catellani reaction including C(sp²)-H functionalization. A one-pot reaction involving both C(sp³)-H and C(sp²)-H

functionalization was also attempted. Our newly developed strategy is suitable for the facile preparation of various analogues because it uses simple starting materials and does not require protecting groups.

Keywords: C-H functionalization • total synthesis • alkaloids • pyrrolophenanthridine • assoanine

Introduction

Pyrrolophenanthridine alkaloids, which can be biogenetically produced by the dehydration and aromatization of lycorine, belong to the Amaryllidaceae family of alkaloids (Figure 1),¹ and assoanine (**1**), which was originally isolated from *Narcissus pseudonarcissus* by Wildman et al.² in 1956, is representative of this class alkaloids.² More than ten congeners, including pratosine (**2**),³ hippadine (**3**),⁴ and dihydroanhydrolycorin (**4**),⁵ have been isolated from plants belonging to the Amaryllidaceae species. Pyrrolophenanthridine alkaloids have been reported to exhibit various biological properties, including acetylcholinesterase inhibitory activity,⁶ anticancer activity,⁷ and anti-tripanosomal activity,⁸ and have consequently received considerable attention from both chemists and biological scientists.¹ A variety of total syntheses have been reported to date for the preparation of pyrrolophenanthridine alkaloids, and these strategies have generally focused on the use of an indole derivative as the starting material for the construction of the biaryl moiety of the alkaloid.⁹ For example, Snieckus and Siddiqui reported the

Suzuki coupling reaction of 7-iodoindoline with 2-formylphenyl boronic acid in the presence of a palladium catalyst to give a pyrrolophenanthridine skeleton, which was subsequently converted to hippadine (**3**).^{9y} Pd-catalyzed cross-coupling reactions have also been used to construct the biaryl moiety of pyrrolophenanthridine alkaloids.^{9d,e,i,s,t,w} Diels-Alder,^{9q,aa} ring expansion,^{9t} anion coupling,^{9r,u} and radical cyclization^{9n,o,s,x} reactions have also been used as key transformations for construction of the biaryl moiety or the phenanthridine skeleton of pyrrolophenanthridine alkaloids.

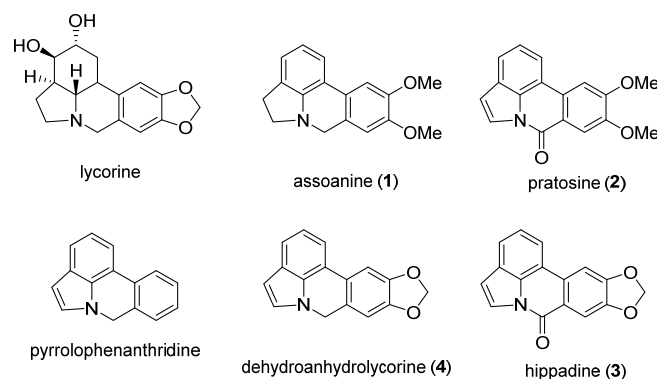


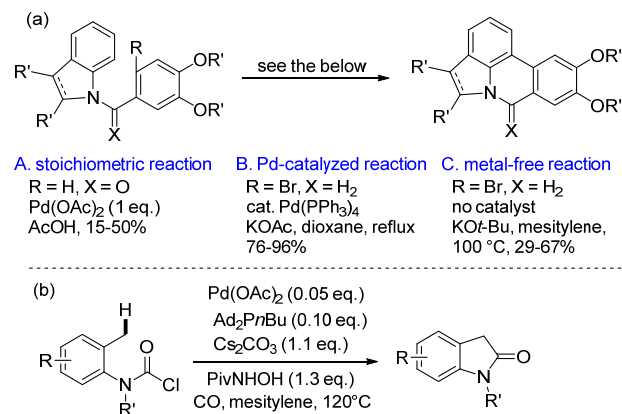
Figure 1. Lycorine and pyrrolophenanthridine alkaloids.

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Carbon-hydrogen bond (C-H) functionalization chemistry has received considerable attention as an innovative method in organic chemistry during the last decade, because it has the potential to simplify synthesis by allowing for the use of ubiquitous C-H

bonds.¹⁰ The popularity of C-H functionalization reactions has grown considerably in recent years, with various groups reporting the concise total syntheses of natural products based on transition metal-catalyzed C-H functionalization strategies.¹¹ As part of their work towards the total synthesis of pyrrolophenanthridine alkaloids, Black et al.^{9v,z} achieved the total synthesis of pratosine (**2**) and hippadine (**3**) in 1989 using a C(sp²)-H functionalization reaction for the construction of the biaryl moiety in these compounds, although a stoichiometric amount of Pd(OAc)₂ was required (Scheme 1 (a), A). Ten years later, Miki et al.^{9c,l} reported a Pd(0)/Pd(II)-catalyzed C(sp²)-H functionalization reaction, which started with the oxidative addition of Pd(0) to an aryl halide, and several groups went on to adopt this method in their own work (Scheme 1 (a), B).^{9g,h,k} In 2012, Bisai et al.^{9a,b} developed a transition-metal-free C(sp²)-H functionalization reaction for the construction of biaryl compounds, which was applied to total synthesis of several pyrrolophenanthridine alkaloids. There have, however, been no reports in the literature concerning the total synthesis alkaloids belonging to this class using a C(sp³)-H functionalization reaction. We recently developed a series of synthetic methods for the construction of several heterocyclic systems, including oxindoles, spirooxindoles, 2-aryl indoles and benzocarbazoles, using a C(sp³)-H functionalization reaction (Scheme 1 (b)).¹² To evaluate the scope and generality of our newly developed C(sp³)-H functionalization method for the construction of oxindoles, we investigated its application to total synthesis of Amaryllidaceae alkaloids.^{12a} Herein, we report a concise synthesis of assoanine (**1**), pratosine (**2**), hippadine (**3**) and dihydroanhydrolycorin (**4**) from simple commercially available starting materials based on the C(sp³)-H functionalization, which could be also be used to prepare various analogues of these compounds.

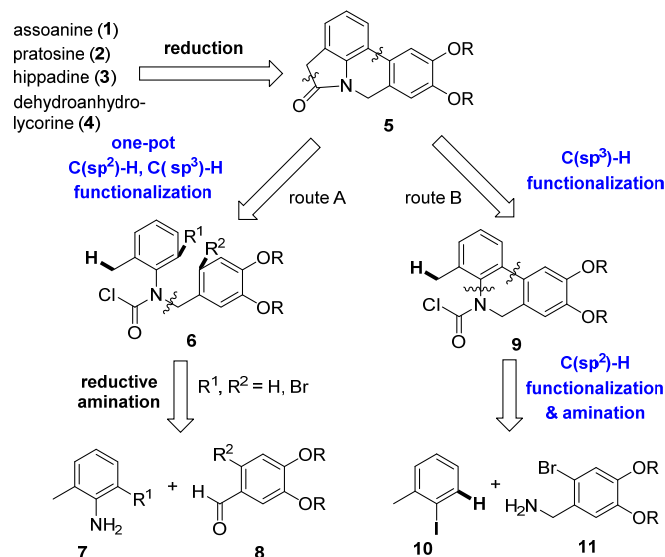


Scheme 1. (a) Reported synthesis of biaryl systems using a C-H functionalization reaction, (b) oxindole formation using a C(sp³)-H functionalization reaction.

Synthetic Plan

Retrosynthetically, it was envisioned that compound **5** could be used as a common intermediate for the synthesis of pyrrolophenanthridine alkaloids, and that this compound could be synthesized using C(sp³)-H and C(sp²)-H functionalization reactions (Scheme 2). For example, the oxindole and phenanthridine rings could be constructed by the C(sp³)-H and C(sp²)-H functionalization reactions of the methyl and phenyl groups, respectively. Because both of these reaction require similar conditions in terms of their Pd(0)/Pd(II) catalytic cycles, the tetracyclic skeleton of **5** could be constructed from carbamoyl chloride **6** according to a one-pot

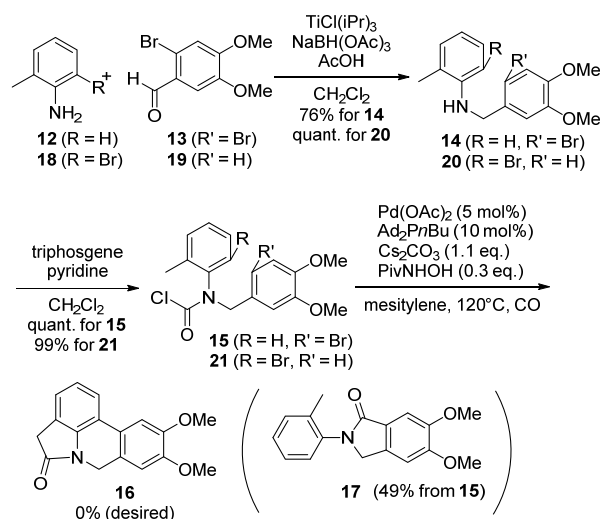
reaction (path A). In contrast, we could use a stepwise strategy for the construction of the lactam ring and the dihydrophenanthrine skeleton from iodotoluene **10** and benzylaniline **11** using C(sp²)-H and C(sp³)-H functionalization reactions. In this case, the lactam ring would have to be constructed during the later stages of the process because the C(sp³)-H functionalization reaction requires higher temperatures than the C(sp²)-H reaction.



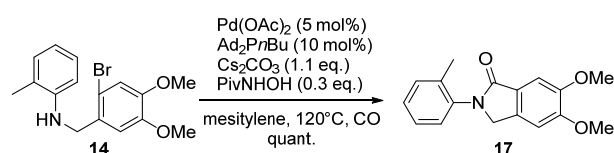
Scheme 2. Retrosynthesis of pyrrolophenanthridine alkaloids based on C(sp³)-H and C(sp²)-H functionalization reactions.

Results and Discussion

We focused our initial efforts on investigating route A, which would provide a concise short-step synthesis involving the challenging double cyclization of carbamoyl chloride **15** or **21**. o-Toluidine (**12**) was coupled with 6-bromoveratraldehyde (**13**) according to McDonald's reductive amination procedure¹³ (Scheme 3). The resulting amine **14** was treated with triphosgene and pyridine to give carbamoyl chloride **15**. The other carbamoyl chloride **21** was also prepared by the same two-step sequence from **18** and **19**. The double cyclization reaction involving the C(sp³)-H and C(sp²)-H functionalization reactions was attempted by the treatment of **15** with Pd(OAc)₂ (5 mol%), Ad₂PnBu (10 mol%), Cs₂CO₃ (1.1 equiv.) and PivNHOH (0.3 equiv.) in mesitylene (0.2 M) at 120 °C under an atmosphere of carbon monoxide.^{12a} Unfortunately, however, this reaction gave lactam **17** in 49% yield instead of the desired product **16**. The by-product **17** was most likely derived from amine **14**, which would have been produced by the oxidative addition of carbamoyl chloride **15** followed by the elimination of CO. Indeed, treatment of amine **14** under the same conditions gave compound **17** quantitatively via the oxidative addition of the aryl bromide followed by insertion of CO (Scheme 4). It was assumed that the oxidative addition of the aryl bromide would be favorable and that the resulting palladium intermediate would assist in the elimination of CO from the carbamoyl chloride. This sequence would allow for the formation of the isooxindole **17** following sequential CO insertion and cyclization reactions.



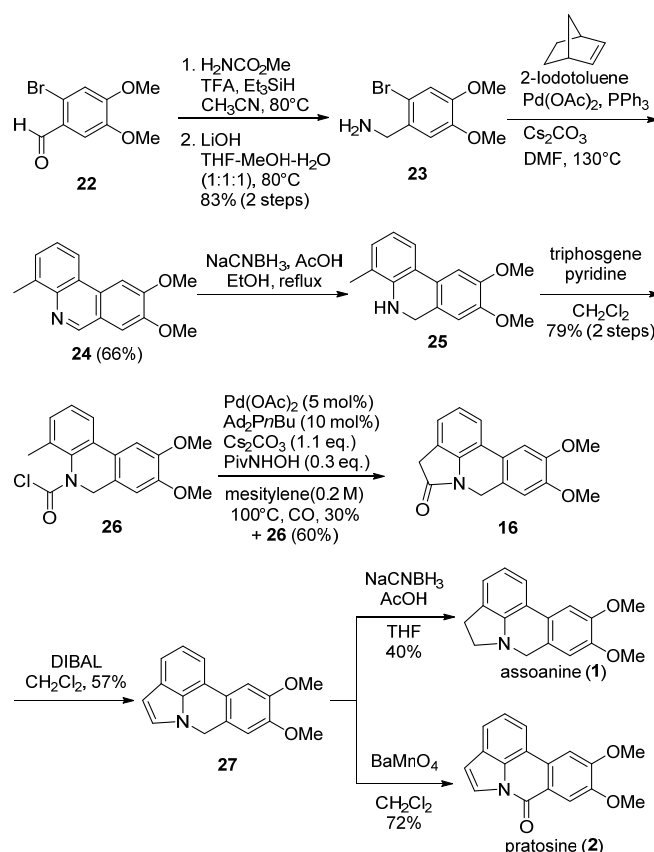
Scheme 3. Attempted one-pot formation of the tetracyclic skeleton.



Scheme 4. Formation of isooxindole **17**.

The carbon-bromide bond was moved from one aryl ring to the other in an attempt to avoid the decomposition of the carbamoyl moiety. However, treatment of carbamoyl chloride **21** under the same conditions gave aniline **20** as the major product (31%), which was formed via the elimination of CO, together with small amounts of several unidentified by-products (Scheme 3). Although compound **21** did not give rise to a four-membered lactam ring, the C(sp³)-H functionalization reaction was probably hampered by the oxidative addition of the aryl bromide followed by the elimination of CO. Based on this result, it was concluded that it would be difficult to suppress the undesired reaction, because the oxidative addition reactions of the carbamoyl chloride and aryl bromide were competitive, and the activation of the C(sp³)-H bond would require a higher temperature than those required of the side reactions.

Based on these limitations, we decided to focus our attention of route B, which would avoid possible complications arising from the unfavorable decomposition of the carbamoyl moiety (Scheme 2). This particular synthesis started from the reductive amination of 6-bromoveratraldehyde (**22**), followed by hydrolysis of the resulting carbamate to give benzylamine **23** in 83% yield over two steps (Scheme 5).¹⁴ Compound **23** was then coupled with 2-iodotoluene **12** using a Catellani reaction with Pd(OAc)₂ (5 mol%), PPh₃ (10 mol%), Cs₂CO₃ (2.1 equiv.), and 2-norbornene (0.5 equiv.) in DMF (0.2 M) at 130 °C under an atmosphere of Ar according to Malacria's procedure.^{15,16} Although our initial attempts to isolate dihydrophenanthridine **25** resulted in low yields because the material was readily oxidized under the purification conditions, phenanthridine **24** was obtained in 66% yield after purification. Subsequent reduction of compound **24** using NaCNBH₄¹⁷ followed by treatment of the resulting amine with triphosgene gave the carbamoyl chloride **26** in 79% yield over two steps.



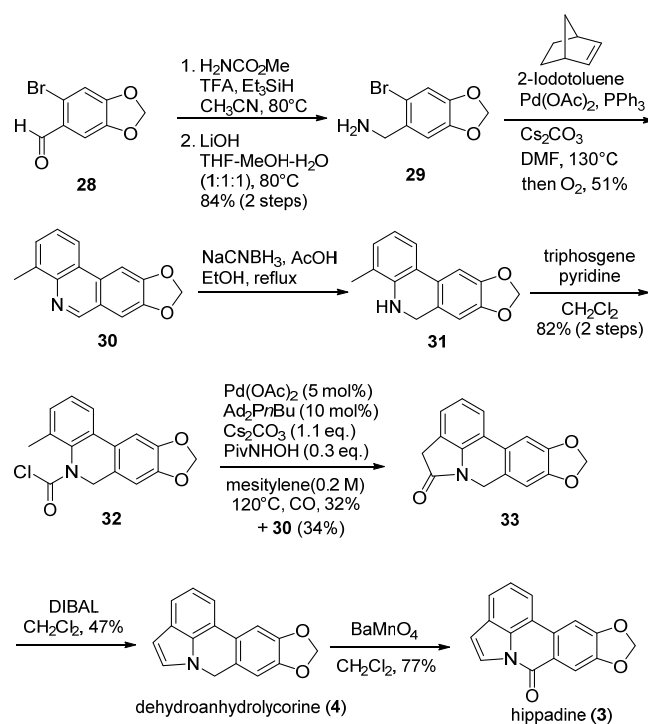
Scheme 5. Total synthesis of assoanine (**1**) and pratosine (**2**).

We then turned our attention to the cyclization of carbamoyl chloride **26** using the C(sp³)-H functionalization reaction. Treatment of **26** with Pd(OAc)₂ (5 mol%), Ad₂PnBu (10 mol%), Cs₂CO₃ (1.1 equiv.), and PivNHOH (0.3 equiv.) in mesitylene (0.2 M) under an atmosphere of CO at 100 °C gave the desired tetracyclic compound **16** (30%) together with a significant amount of the compound **24** (60%), which was presumably derived from the elimination of CO and aerial-oxidation.¹⁸ Although an extensive period of reaction screening (i.e., palladium sources, ligands, bases and additives) did not lead to an improvement in the yield of the product, compound **24** could be recycled following its separation from the product by silica gel column chromatography. Because the carbamoyl moiety was fixed by the rigid tricyclic skeleton, the C-H bond of the methyl group became distant from the palladium center compared with the corresponding derivatives of phenyl carbamoyl chloride, and the elimination of CO consequently became competitive.

With the common intermediate **16** in hand, we investigated the formation to the natural products by adjustment of oxidation level. The reduction of **16** with DIBAL-H gave dehydroassoanine **27** in 57% yield, which was oxidized with BaMnO₄ to give pratosine (**2**) in 72% yield.^{9m} In contrast, assoanine (**1**) was synthesized in 40% yield by the reduction of **27** with NaCNBH₃ in AcOH.^{9b} The spectroscopic data for these compounds, including the high-resolution mass spectra of synthetic pratosine and assoanine, were found to be in agreement with the previously reported data for these compounds.^{2,3,9f,h,r,u}

The established synthetic route was applied to the synthesis of hippadine (**3**) and dehydroanhydrolicorine (**4**). Commercially available 6-bromopiperonal **28** was converted to benzyl amine **29** in

84% yield over two steps (Scheme 6). Compound **29** was then coupled to 2-iodotoluene **12** using a Catellani reaction followed by an oxidation reaction to give phenanthridine **30** in 51% yield. Because dihydrophenanthridine **31** was not readily oxidized in the presence of air in the same way as **25**, it was necessary to expose this compound to an oxygen atmosphere to affect the one-pot procedure. Reduction with NaCNBH₃ followed by the treatment of the resulting amine with triphosgene gave carbamoyl chloride **32** in 82% yield over two steps. In a similar manner to the synthesis of assoanine, the cyclization of carbamoyl chloride **32** proceeded smoothly following the activation of the C(sp³)-H bond to give the desired tetracyclic compound **33** and phenanthridine **30**, which is recyclable, in 32 and 34% yields, respectively. The tetracyclic compound **33** was converted to hippadine (**3**) by reduction with DIBAL-H followed by the oxidation of dehydroanhydrolycorine (**4**). The spectroscopic data for the synthetic materials **3** and **4** were in good agreement with the previously reported data for these compound.^{4,5,9f,r,s} The established synthetic route, which is short and concise because it does not require the use of protecting groups, could be used to provide facile access to various analogues from simple starting material.



Scheme 6. Total synthesis of hippadine (**3**) and dehydroanhydrolycorine (**4**).

Conclusion

We have accomplished the total synthesis of assoanine (**1**), pratosine (**2**), hippadine (**3**) and dehydroanhydrolycorine (**4**) using C-H activation chemistry. The tetracyclic skeleton **5** was constructed in a stepwise manner using a C(sp³)-H functionalization reaction for the oxindole skeleton and Catellani reaction including a C(sp²)-H functionalization reaction to complete the system. Our newly developed route is suitable for the facile preparation of related analogues because it uses simple starting materials and does not require the use of protecting groups. Our synthesis, which is comparable in many ways to those previously reported in this area because it allows for the rapid preparation of analogues related to

the target compounds, and represents a new area of C(sp³)-H functionalization chemistry.

Experimental Section

General. All non-aqueous reactions were carried out under a positive atmosphere of argon in oven-dried glassware. Analytical thin-layer chromatography (TLC) was performed with Silica gel 60 TLC plates (Merck). Silica gel column chromatography was performed with Kanto silica gel 60 (particle size, 63–210 μm) and Fuji silylsia Chromatorex BW-300. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a JEOL JNM-ECA 500 spectrometer at 500 MHz or a JEOL JNM-AL 400 at 400 MHz. Chemical shifts have been reported relative to Me₄Si (δ 0.00 ppm) in CDCl₃, and CHDCl₂ (δ 5.32 ppm) in CD₂Cl₂. The multiplicities of the signals have been indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on a JEOL JNM-ECA 500 at 126 MHz or a JEOL JNM-AL 400 at 100 MHz. The chemical shifts have been reported relative to residual CDCl₃ and CD₂Cl₂ (δ 77.0 and 53.8 ppm), respectively. Infrared spectra were recorded on a FT/IR-4100 Fourier-transform infrared ATR attenuated total reflectance spectrometer (JASCO). Low and High resolution mass spectra were recorded on a JEOL MS700 mass spectrometer.

Oxindole 16: Carbamoyl chloride **26** (59.4 mg, 0.19 mmol) was mixed with Pd(OAc)₂ (2.3 mg, 0.010 mmol), Ad₂PnBu (6.7 mg, 0.019 mmol), Cs₂CO₃ (67.1 mg, 0.21 mmol) and PivNH₂OH (6.6 mg, 0.056 mmol), and the resulting mixture was purged under an atmosphere of CO. Mesitylene (1 mL) was then added to the reaction, and the resulting mixture was stirred at 100 °C for 1 hour. The mixture was then filtered through a pad of celite and the filtrate collected and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (hexane/AcOEt = 1/1 – v/v and then CH₂Cl₂/AcOEt = 9/1 to 8/2 – v/v) to give oxindole **16** (15.7 mg, 30%) as a white solid and phenanthridine **24** (28.5 mg, 60%): ¹H NMR (400 MHz, CDCl₃) δ 7.48 (1H, d, *J* = 7.6 Hz), 7.24 (1H, s), 7.08 (1H, d, *J* = 7.6 Hz), 7.01 (1H, t, *J* = 7.0 Hz), 6.63 (1H, s), 5.01 (2H, s), 3.97 (3H, s), 3.91 (3H, s), 3.54 (2H, s); ¹³C NMR (101 MHz, CD₂Cl₂) δ 174.7, 149.9, 149.3, 140.2, 123.7, 123.5, 122.6, 122.0, 121.6, 119.9, 117.3, 110.8, 105.9, 56.3, 56.2, 43.2, 36.6; IR (ATR) 3021, 2986, 2836, 1696, 1627, 1521, 1495, 1482, 1467, 1443, 1359, 1242, 1212 cm⁻¹; HRMS (FAB) *m/z* calcd for C₁₇H₁₆NO₃ [M+H]⁺ 282.1130; found: 282.1135.

Compound 27: Oxindole **16** (86.4 mg, 0.307 mmol) was dissolved in CH₂Cl₂ (3.6 mL) under an atmosphere of argon, and the resulting solution was cooled to 0 °C before being treated with a 1 M solution of DIBAL in toluene (1.95 mL, 1.95 mmol). The reaction mixture was stirred at 0 °C for 2 hours, and then quenched by the addition of 2 M aqueous NaOH. The resulting mixture was extracted with CHCl₃ and the combined organics were washed with brine and dried over Na₂SO₄ before being filtered and concentration under reduced pressure to give a residue, which was purified by silica gel column chromatography (hexane/CHCl₃ = 1/1) to give **27** (46.1 mg, 57%) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 7.44 (1H, d, *J* = 8.0 Hz), 7.37 (2H, d, *J* = 7.6 Hz), 7.14 (1H, d, *J* = 3.6 Hz), 7.06 (1H, t, *J* = 7.6 Hz), 6.65 (1H, s), 6.53 (1H, d, *J* = 2.8 Hz), 5.52 (2H, s), 3.99 (3H, s), 3.92 (3H, s); ¹³C NMR (101 MHz, CDCl₃) δ 148.9, 148.7, 133.0, 125.9, 125.7, 122.7, 122.5, 120.3, 119.9, 118.6, 112.6, 109.8, 105.5, 102.4, 56.0, 56.0, 47.6; IR (ATR) 2933, 2854, 1673, 1608, 1525, 1464, 1392, 1337, 1254, 1212 cm⁻¹; HRMS (FAB) *m/z* calcd for C₁₇H₁₆NO₂ [M+H]⁺ 266.1181; found: 266.1161.

Pratosine (2): To a solution of compound **27** (21.6 mg, 0.0814 mmol) in CH₂Cl₂ (1.9 mL) was added BaMnO₄ (209 mg, 0.814 mmol) under an atmosphere of argon, and the resulting mixture was stirred at room temperature for 2.5 hours. The mixture was then filtered through a pad of celite and the filtrate was collected and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (CH₂Cl₂ and then CH₂Cl₂/AcOEt = 20/1) to give pratosine **2** (16.4 mg, 72%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 8.07 (1H, d, *J* = 4.0 Hz), 8.02 (1H, s), 7.99 (1H, d, *J* = 7.6 Hz), 7.76 (1H, d, *J* = 7.2 Hz), 7.67 (1H, s), 7.49 (1H, t, *J* = 7.4 Hz), 6.91 (1H, d, *J* = 3.2 Hz), 4.13 (3H, s), 4.07 (3H, s); ¹³C NMR (101 MHz, CDCl₃) δ 158.4, 153.7, 149.7, 131.1, 129.5, 128.5, 123.9, 123.5, 122.4, 120.8, 118.0, 116.7, 110.7, 110.1, 103.8, 56.29, 56.25; IR (ATR) 3010, 2837, 1665, 1602, 1526, 1507, 1440, 1362, 1308, 1270, 1216 cm⁻¹; HRMS (FAB) *m/z* calcd for C₁₇H₁₄NO₃ [M+H]⁺ 280.0974; found: 280.0965.

Assoanine (1): To a solution of compound **27** (20.7 mg, 0.078 mmol) in THF (1.0 mL) was added AcOH (0.3 mL) and NaCNBH₃ (0.72 mmol), and the resulting mixture was stirred at room temperature for 6 hours. The reaction mixture was then neutralized with 1 M aqueous NaOH and extracted with AcOEt. The combined organic phases were washed with brine and dried over Na₂SO₄ before being filtered and concentration under reduced pressure to give a residue, which was purified by silica gel column chromatography (hexane/AcOEt = 5/1) to give assoanine **1** (8.4 mg, 40%) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 7.33 (1H, d, *J* = 8.0 Hz), 7.19 (1H, s), 7.01 (1H, d, *J* = 6.8 Hz), 6.77 (1H, t, *J* = 7.6 Hz), 6.66 (1H, s), 4.12 (2H, s), 3.95 (3H, s), 3.90 (3H, s), 3.35 (2H, t, *J* = 8.2 Hz), 3.03 (2H, t, *J* = 7.8 Hz); ¹³C NMR (101 MHz, CDCl₃) δ

149.6, 148.6, 148.4, 128.5, 124.7, 124.3, 123.3, 119.6, 119.3, 119.0, 110.3, 105.4, 56.03, 56.01, 55.4, 53.2, 29.0; IR (ATR) 2924, 1609, 1520, 1472, 1406, 1346, 1250 cm⁻¹; HRMS (FAB) *m/z* calcd for C₁₇H₁₈NO₂ [M+H]⁺ 268.1338; found: 268.1329.

Oxindole 33: Carbamoyl chloride **32** (179 mg, 0.59 mmol) was mixed with Pd(OAc)₂ (6.6 mg, 0.029 mmol), Ad₂PnBu (21 mg, 0.059 mmol), Cs₂CO₃ (213 mg, 0.65 mmol) and PivNH₂OH (21 mg, 0.18 mmol), and the resulting mixture was purged under an atmosphere of CO. Mesitylene (3 mL) was then added to the reaction, and the resulting mixture was stirred at 120 °C for 1.5 hours before being filtered through a pad of celite. The filtrate was collected and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (hexane/AcOEt = 3/1 and then CH₂Cl₂/AcOEt = 9/1) to give oxindole **33** (49.9 mg, 32%) as a yellow solid, and phenanthridine **30** (53.8 mg, 34%): ¹H NMR (500 MHz, CD₂Cl₂) δ 7.41 (1H, d, *J* = 7.0 Hz), 7.22 (1H, s), 7.07 (1H, d, *J* = 7.0 Hz), 6.96 (1H, t, *J* = 7.7 Hz), 6.64 (1H, s), 5.99 (2H, s), 4.92 (2H, s), 3.47 (2H, s); ¹³C NMR (126 MHz, CD₂Cl₂) δ 174.6, 148.4, 148.3, 140.2, 123.7, 123.6, 123.4, 123.2, 122.7, 120.1, 117.3, 107.9, 102.8, 102.1, 43.7, 36.6; IR (ATR) 3042, 2922, 1698, 1632, 1510, 1474, 1351, 1255, 1231, 1209 cm⁻¹; HRMS (FAB) *m/z* calcd for C₁₆H₁₂NO₃ [M+H]⁺ 266.0817; found: 266.0817.

Dehydroanhydrolicorine (4): Oxindole **33** (43.8 mg, 0.165 mmol) was dissolved in CH₂Cl₂ (2 mL) under an atmosphere of argon, and the resulting solution was cooled to 0 °C before being treated with a 1 M solution of DIBAL in toluene (0.99 mL, 0.99 mmol). The reaction mixture was then stirred at 0 °C for 3 hours before being quenched by the addition of 2 M aqueous NaOH. The residue was extracted with CHCl₃ and the combined organics were washed with brine and dried over Na₂SO₄ before being filtered and concentration under reduced pressure to give a residue, which was purified by silica gel column chromatography (hexane/CHCl₃ = 1/1) to give dehydroanhydrolicorine **4** (19.9 mg, 48%) as a red solid: ¹H NMR (400 MHz, CDCl₃) δ 7.44 (1H, d, *J* = 8.0 Hz), 7.37 (1H, s), 7.32 (1H, d, *J* = 7.6 Hz), 7.12 (1H, d, *J* = 3.2 Hz), 7.05 (1H, t, *J* = 7.4 Hz), 6.65 (1H, s), 6.52 (1H, d, *J* = 3.2 Hz), 6.00 (2H, s), 5.50 (2H, s); ¹³C NMR (101 MHz, CDCl₃) δ 147.6, 147.5, 133.0, 125.9, 125.7, 124.2, 123.8, 120.4, 120.0, 118.6, 112.9, 107.1, 102.9, 102.5, 101.3, 48.1; IR (ATR) 2902, 1730, 1657, 1502, 1485, 1461, 1339, 1242 cm⁻¹; HRMS (FAB) *m/z* calcd for C₁₆H₁₂NO₂ [M+H]⁺ 250.0868; found: 250.0855.

Hippadine (3): To a solution of oxindole **33** (12.3 mg, 0.0493 mmol) in CH₂Cl₂ (1.4 mL) was added BaMnO₄ (126 mg, 0.493 mmol) under an atmosphere of argon, and the resulting mixture was stirred at room temperature for 2.5 hours. The reaction mixture was then filtered through a pad of celite and the filtrate was collected and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (hexane/CH₂Cl₂ = 2/1) to give hippadine **3** (10.0 mg, 77%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 8.05 (1H, d, *J* = 3.6 Hz), 7.99 (1H, s), 7.93 (1H, d, *J* = 7.6 Hz), 7.76 (1H, d, *J* = 8.0 Hz), 7.67 (1H, s), 7.48 (1H, t, *J* = 7.8 Hz), 6.90 (1H, d, *J* = 3.2 Hz), 6.17 (2H, s); ¹³C NMR (101 MHz, CDCl₃) δ 158.2, 152.6, 148.5, 131.6, 130.9, 128.4, 124.0, 123.5, 122.6, 122.5, 118.4, 116.7, 110.8, 108.0, 102.3, 101.7; IR (ATR) 3152, 2922, 1670, 1618, 1526, 1477, 1457, 1392, 1366, 1347, 1310, 1286, 1244 cm⁻¹; HRMS (FAB) *m/z* calcd for C₁₆H₁₀NO₃ [M+H]⁺ 264.0661; found: 264.0647.

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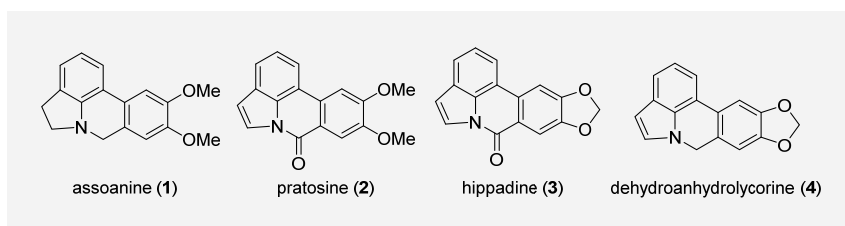
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Synthesis of
Pyrrolophenanthridine alkaloids
based on C(sp³)-H and C(sp²)-H
functionalization reactions



Assoanine (1), pratosine (2),
 hippadine (3) and dehydroanhydro-
 lycorine (4) belong to the
 pyrrolophenanthridine family of
 alkaloids, which are isolated from
 plants of Amaryllidaceae species.

These alkaloids have been
 successfully synthesized using C-H
 activation chemistry. Their
 tetracyclic skeletons were
 constructed in a stepwise manner by
 C(sp³)-H functionalization and a
 Catellani reaction involving C(sp²)-
 H functionalization.